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International application number: PCT/GB05/001099

International filing date: 23 March 2005 (23.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0406757.5
Filing date: 26 March 2004 (26.03.2004)

Date of receipt at the International Bureau: 09 May 2005 (09.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



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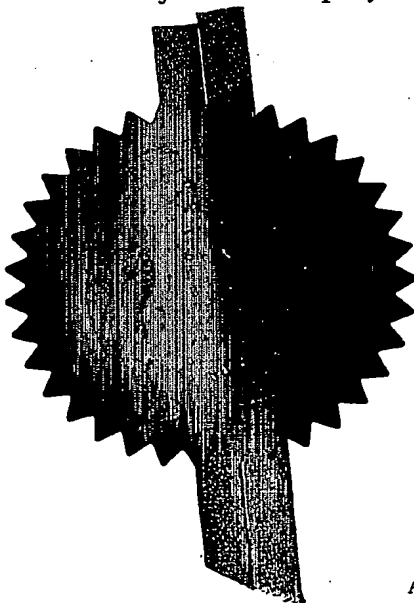
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Signed

William Morell

Dated

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Request for grant of a patent

(See the notes on the back of this form. You may also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1. Your reference	SMC 60647/GB/P1		
2. Patent application number (The Patent Office will fill in this part)	0406757.5		26 MAR 2004
3. Full name, address and postcode of the or of each applicant (underline all surnames)	Avecia Limited Hexagon House Blackley Manchester, M9 8ZS		
Patents ADP number (if you know it)	07764137001		
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom		
4. Title of the invention	Process and Compounds		
5. Name of your agent (if you have one)	GAIRNS, Raymond Stevenson		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Avecia Limited Hexagon House PO Box 42 Blackley Manchester M9 8ZS		
Patents ADP number (if you know it)	69834720001		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day / month / year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)	
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if)			
a) any applicant named to part 3 is not an inventor, or			
b) there is an inventor who is not named as an applicant, or			
c) any named applicant is a corporate body.			
See note (d)			

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Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description

Claim(s)

Abstract

Drawing(s)

6

4

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of Invention and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 2/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

over letter

11.

I/We request the grant of a patent on the basis of this application.

Signature *K. M. Pinder* Date 26-3-04
Avecia Limited Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom

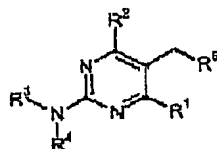
K.M.Pinder/G.Terry 0161 721 1361/2

Warning

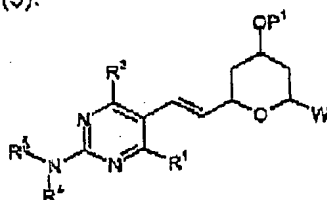
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Notes

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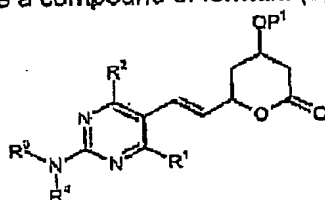


wherein R^3 represents a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and R^6 represents $(PR^7R^8)^+X^-$ or $P(=O)R^7R^8$ in which X is an anion and R^7 and R^8 each independently is an alkyl, aryl, alkoxy or aryloxy group, preferably a phenyl group,
to give a compound of formula (5):



wherein R^3 represents a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group,

d) when W represents $-OP^2$, removing any P^2 protecting group and oxidising the compound of formula (5) to give a compound of formula (6):



and

e) subjecting the compound of formula (5) when W represents $=O$, or compound of formula (6) to ring-opening, removal of any P^1 protecting groups, and optionally removing any additional protecting groups to give a compound of formula (7).

In step (e), any P^1 protecting groups and any additional protecting groups may be removed individually or together and prior to ring opening, during ring opening or after ring opening of the compounds of formula (5) or (6).

Protecting groups which may be represented by P^1 and P^2 include alcohol protecting groups, examples of which are well known in the art. Particular examples include tetrahydropyranyl, benzyl and methyl groups. Preferred protecting groups are silyl

groups, for example triaryl- and especially trialkylsilyl groups. Especially preferred examples are trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenyl groups.

Protecting groups which may be represented by P^1 and P^2 may be the same or different. When the protecting groups P^1 and P^2 are different, advantageously this may allow for the selective removal of only P^1 or P^2 . Preferably, when the protecting groups P^1 and P^2 are different, P^1 is a silyl group and P^2 is a methyl group.

Protecting groups which may be represented by R^3 and R^4 include amine protecting groups, examples of which are well known in the art. Particular examples include benzyl groups, carbamates (such as CBZ, Boc, Fmoc), phosphate, thiophosphate, silyl groups and, when R^3 and R^4 together are a single protecting group, an imine group.

Hydroxylation of compounds of formula (1) can be achieved by methods known in the art for displacing a halo group with a hydroxide source. Preferably, the process comprises contacting the compound of formula (1) with a source of hydroxide. Hydroxide sources include hydroxide salts, especially ammonium or alkali metal hydroxides, particularly lithium, sodium or potassium hydroxide, and various aqueous media such as water in the presence of basic media such as N-methylpyrrolidinone, HMPA, Al_2O_3 , $CaCO_3$, Na_2CO_3 , K_2CO_3 or $KO_2/18$ -crown-6, silver salts such as $AgNO_3$ or Ag_2O , or oxidants such as perbenzoic acid. A particularly preferred process comprises contacting the compound of formula (1) with 5 molar equivalents of KOH in the presence of dimethylsulfoxide solvent at a temperature of, for example, about $50^\circ C$.

Alternatively, hydroxylation may be achieved by first displacing the halogen with a leaving group such as acetate, triflate or sulphate optionally in the presence of a silver salt, then displacing the leaving group with a hydroxide source. A particularly preferred process comprises contacting the compound of formula (1) with 3 molar equivalents of NaOAc in the presence of dimethylformamide solvent and tetra-n-butylammonium chloride at a temperature of, for example, about $100^\circ C$, isolating the acetyl compound and contacting with potassium carbonate in the presence of methanol solvent and at a temperature of, for example, about $0^\circ C$.

Oxidation of compounds of formula (2) can be achieved using oxidation systems known in the art for the oxidation of alcohols, especially those known in the art for the oxidation of primary alcohols. Examples include oxidation with Dess-Martin periodinane, bromine, Swern oxidation or various metal based oxidations such as Fétizon reagent, manganate based reagents, and chromate based reagents such as Collins reagent. Swern oxidation is preferred. When Swern oxidation is employed, preferred conditions comprise the use of dimethyl sulphoxide and oxalyl chloride or bromine in a solvent such as dichloromethane or dichloromethane/THF mixtures, at reduced temperature, such as from 0 to $-100^\circ C$, preferably -50 to $-80^\circ C$. Preferably, reagents are added at reduced temperature, such as -30 to $-80^\circ C$, and then once all reagents are added, the reaction mixture is allowed to warm to 15 to $20^\circ C$.

The coupling of the compound of formula (3) with the compound of formula (4) may employ conditions analogous to those given in WO01/85702 for the corresponding coupling of a compound of formula (4). The conditions preferably comprise refluxing the compounds of formula (3) and (4) in a hydrocarbon solvent, such as toluene or cyclohexane, or mixtures thereof, followed by contact with aqueous acid, such as aqueous HCl.

Alkyl, aryl, alkoxy or aryloxy groups which may be represented by R^7 and R^8 include C_{1-6} alkyl groups, such as methyl and ethyl groups, C_{6-12} aryl groups, such as phenyl, tolyl or naphthyl, C_{1-6} alkoxy groups, such as ethoxy groups, and C_{6-12} aryloxy groups such as phenoxy groups.

Anions which may be represented by X include halide.

R^6 preferably is $P(=O)R^7R^8$ where R^7 and R^8 each independently is an alkyl, aryl, alkoxy or aryloxy group, preferably a phenyl group.

When W represents OP^2 , the protecting group may be removed to form a hydroxy group by methods known in the art for the removal of the given protecting group. For example, silyl protecting groups may be removed by contact with a source of fluoride ion, such as tetrabutylammonium fluoride.

Oxidation of compounds formed by deprotection of compounds wherein W represents $-OP^2$ may employ conditions known in the art for the oxidation of pyranols to pyranones, and include those given in "Comprehensive Organic Transformations", R.C. Larock, 2nd Ed (1999) p 1670, published by Wiley VCH, incorporated herein by reference. Preferred oxidation systems include Ag_2CO_3 /Cellite, especially Cellite J2, bromine or Swern.

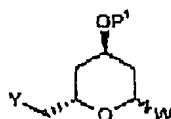
Ring opening of the compounds of formula (5), when W represent $=O$ or formula (6) may employ conditions known in the art for ring opening of a pyranone. Preferably, the ring is opened by contact with a base, such as sodium hydroxide. Conveniently, polar solvents are employed, for example methanol, acetonitrile, tetrahydrofuran or mixtures thereof.

Remaining protecting groups may be removed by methods known in the art for the removal of the given protecting group. For example, silyl protecting groups may be removed by contact with a source of fluoride ion, such as tetrabutylammonium fluoride.

It will also be recognised that compounds of formulae (2), (3) and (5) may also be subjected to oxidation (when W represents $-OH$) or deprotection and oxidation (when W represents $(-O-$ protecting group) to form the corresponding compound wherein W represents $=O$.

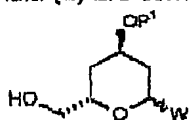
Preferred compounds of formula (1) are compounds of formula:

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wherein W, P¹ and Y are as previously described.

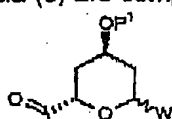
Preferred compounds of formula (2) are compounds of formula:



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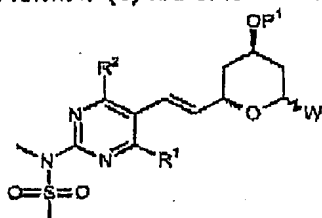
wherein W and P¹ are as previously described.

Preferred compounds of formula (3) are compounds of formula:



wherein W and P¹ are as previously described.

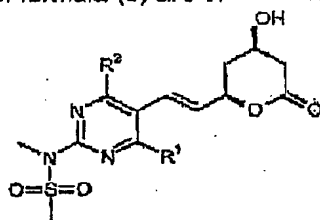
Preferred compounds of formula (5) are of formula:



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wherein R¹, R², W and P¹ are as previously described.

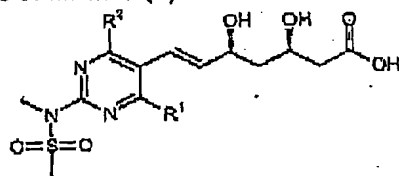
Preferred compounds of formula (6) are of formula:



wherein R¹ and R² are as previously described.

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Preferred compounds of formula (7) are of formula:



wherein R¹ and R² are as previously described.

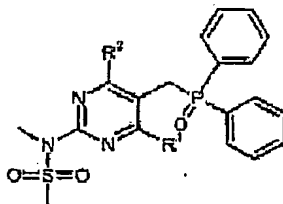
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6.

Compounds of formula (7) are advantageously converted to pharmaceutically acceptable salts, especially their calcium salts (for example WO01/60804).

Compounds of formula (4) are advantageously prepared by the methods given in WO00/49014 and WO01/85702. Particularly preferred compounds of formula (4) are compounds of formula:



Compounds of formula (1) are advantageously prepared by enzyme catalysed condensation of acetaldehyde and 2-haloacetaldehyde, for example using the method given in US patent 5,795,749.

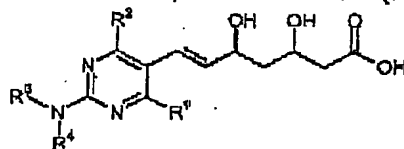
Compounds of formulae (2) and (3) and, when W is OP^3 , formula (5) form further aspects of the present invention.

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CLAIMS

1. a process for the preparation of a compound of formula (7):



wherein

R¹ represents an alkyl group, such as a C₁₋₆ alkyl group, and preferably an isopropyl group;

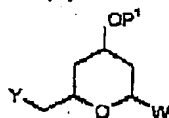
R² represents an aryl group, preferably a 4-fluorophenyl group;

R³ represents hydrogen, a protecting group or an alkyl group, such as a C₁₋₆ alkyl group, and preferably a methyl group; and

R⁴ represents hydrogen, a protecting group or a SO₂R⁵ group where R⁵ is an alkyl group, such as a C₁₋₆ alkyl group, and preferably a methyl group,

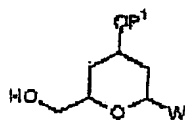
which comprises

- a) hydroxylating a compound of formula (1):

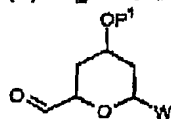


wherein Y represents a halo group, preferably Cl or Br; P¹ represents hydrogen or a protecting group, and W represents =O or -OP², in which P² represents hydrogen or a protecting group,

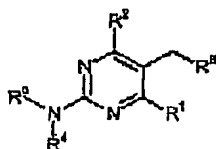
to give a compound of formula (2):



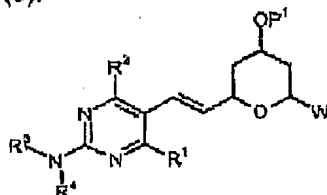
- b) oxidising the compound of formula (2) to give a compound of formula (3):



- c) coupling the compound of formula (3) with a compound of formula (4):

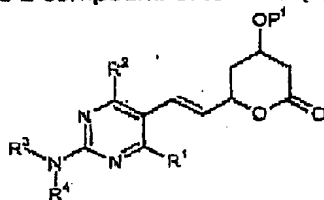


wherein R^2 represents a protecting group or an alkyl group, such as a C_{1-8} alkyl group, and preferably a methyl group; R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-8} alkyl group, and preferably a methyl group; and R^6 represents $(PR^7R^8)^+X^-$ or $P(=O)R^7R^8$ in which X is an anion and R^7 and R^8 each independently is an alkyl, aryl, alkoxy or aryloxy group, preferably a phenyl group, to give a compound of formula (5):



wherein R^2 represents a protecting group or an alkyl group, such as a C_{1-8} alkyl group, and preferably a methyl group; and R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-8} alkyl group, and preferably a methyl group,

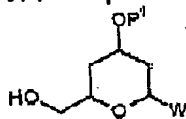
d) when W represents $-OP^2$, removing any P^2 protecting group and oxidising the compound of formula (5) to give a compound of formula (6):



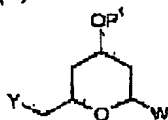
and

e) subjecting the compound of formula (5) when W represents $=O$, or compound of formula (6) to ring-opening, removal of any P^1 protecting groups, and optionally removing any additional protecting groups to give a compound of formula (7).

2. A process for the preparation of a compound of formula (2):



hydroxylating a compound of formula (1):

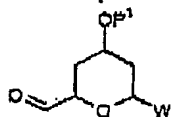


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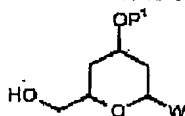
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wherein Y represents a halo group, preferably Cl or Br; P¹ represents hydrogen or a protecting group, and W represents =O or -OP², in which P² represents hydrogen or a protecting group.

3. A process for the preparation of a compound of formula (3):

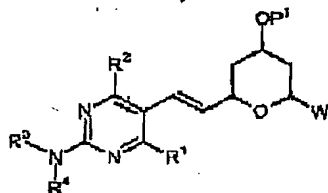


which comprises oxidation of a compound of formula (2):

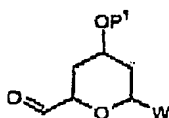


wherein P¹ represents hydrogen or a protecting group, and W represents =O or -OP², in which P² represents hydrogen or a protecting group.

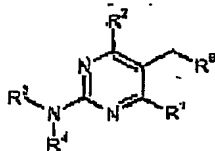
4. A process for the preparation of a compound of formula (5):



which comprises coupling the compound of formula (3):



with a compound of formula (4):



wherein

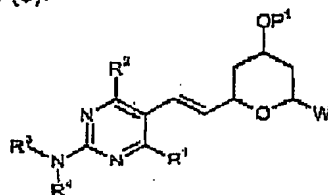
R¹ represents an alkyl group, such as a C₁₋₆ alkyl group, and preferably an isopropyl group;

R² represents an aryl group, preferably a 4-fluorophenyl group;

R³ represents a protecting group or an alkyl group, such as a C₁₋₆ alkyl group, and preferably a methyl group;

R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and
 R^6 represents $(PR^7R^8)^+X^-$ or $P(=O)R^7R^8$ in which X is an anion and R^7 and R^8 each independently is an alkyl, aryl, alkoxy or aryloxy group, preferably a phenyl group,
 R^2 represents hydrogen or a protecting group; and
 W represents $=O$ or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

6. A compound of formula (5):



wherein

R^5 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;
 R^2 represents an aryl group, preferably a 4-fluorophenyl group;
 R^3 represents hydrogen, a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group;
 R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group;
 P^1 represents hydrogen or a protecting group; and
 W represents $=O$ or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

GAIRNS, Raymond, Stevenson
Avecia Pharmaceuticals limited
Intellectual Property Group
PO Box 42
Hexagon Tower
Blackley, Manchester M9 8ZS
ROYAUME-UNI

Date of mailing (day/month/year) 25 May 2005 (25.05.2005)	
Applicant's or agent's file reference SMC 60647/WO	IMPORTANT NOTIFICATION
International application No. PCT/GB05/001099	International filing date (day/month/year) 23 March 2005 (23.03.2005)
International publication date (day/month/year)	Priority date (day/month/year) 26 March 2004 (26.03.2004)
Applicant AVECIA PHARMACEUTICALS LIMITED et al	

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- (If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable)* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
26 March 2004 (26.03.2004)	0406757.5	GB	09 May 2005 (09.05.2005)

The International Bureau of WIPO
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Authorized officer

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